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EDITORIAL

Alveolar gas equation and its clinical implications

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The delivery of oxygen to tissues in the body occurs through a process where the partial pressure of oxygen progressively decreases, known as the oxygen cascade (Fig. 1). The first steps include ventilation, which moves oxygen from the atmosphere to the alveoli; gas exchange, where oxygen diffuses from the alveoli to the pulmonary capillaries; and systemic circulation, where the arteries deliver oxygen to the tissues [1].

Hypoxemia, defined as a reduced arterial oxygen partial pressure (P_{aO_2}), results from abnormalities in the first two steps. The alveolar oxygen partial pressure (P_{AO_2}) and the alveolar–arterial gradient (A–a gradient; calculated by $P_{AO_2} - P_{aO_2}$) help distinguish abnormal ventilation resulting in hypoxemia from impaired gas exchange. Hypoxemia with reduced P_{AO_2} suggests ventilation problems, whereas a preserved P_{AO_2} with a widened A–a gradient indicates impaired gas exchange.

Since direct measurement of P_{AO_2} is not feasible, the alveolar gas equation (AGE) provides an essential framework for approaching and treating hypoxemia, knowing that normalizing physiological variables always need a thoughtful approach [2]. In this article, we first review the equation, detailing the four determinants of P_{AO_2} and how abnormalities in each can lead to hypoxemia. We discuss the application of P_{AO_2} and A–a gradient in evaluating hypoxemia with a series of examples.

Derivation and application

The AGE is expressed as:

$$P_{AO_2} = \left[F_{IO_2} \times \left(P_B - P_{H_2O}\right)\right] - \left(P_{aCO_2} / \mathrm{RER}\right)$$

where P_B is ambient barometric pressure, P_{H_2O} is the water vapor pressure in the alveolus, F_{IO_2} is the fraction of inspired oxygen, P_{aCO_2} is the arterial partial pressure of carbon dioxide, and RER is the respiratory exchange ratio, defined as the ratio of carbon dioxide elimination (V_{CO_2}) to oxygen uptake (V_{O_2}) through the alveoli.

The inspired air becomes fully humidified as it passes through the upper airways, protecting the bronchial epithelium downstream. The resulting P_{H_2O} is relatively constant at 47 mmHg at body temperature. An individual breathing room air (F_{IO_2} 0.21) at sea level (P_B 760 mmHg), with P_{aCO_2} of 40 mmHg and usual RER of 0.8 will have P_{AO_2} approximating 100 mmHg. Because of normal physiologic right-to-left shunt, the resulting P_{aO_2} is around 95 mmHg. Deviations of any of these four variables (F_{IO_2}, P_B, P_{aCO_2}, and the RER) result in a reduced P_{AO_2}, leading to the occurrence of hypoxemia.

Fraction of inspired oxygen

Low F_{IO_2} is an uncommon cause of hypoxemia, occurring with breathing in enclosed environments. As an illustration, a recent study simulating avalanche snow burial demonstrated that hypoxemia develops rapidly as F_{IO_2} decreases in the air pocket around the mouth. F_{ICO_2} concurrently increases, resulting in hypercapnia and further reducing P_{AO_2} (see below). Flushing the air pocket with surrounding air prevented hypoxemia [3].

Increasing F_{IO_2} remains the most immediate intervention to correct hypoxemia by increasing P_{AO_2}. The actual F_{IO_2} delivered to the patient can be difficult to estimate in patients without an invasive airway, limiting the accurate calculation of P_{AO_2}, especially with low-flow oxygen cannulas and Venturi masks, as patients' inspiratory flow relative to delivered flow entrains ambient air [4].

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Location	Atmosphere	Airway	Alveolus	Pulmonary capillary	Artery	Tissue & vein
Determinant	Fraction of inspired oxygen	Water vapor pressure	Alveolar ventilation	Diffusion capacity	Shunt	Blood flow
	Barometric pressure		Oxygen consumption	Ventilation/ perfusion ratio		Metabolism

Alveolar gas equation:

$$P_{AO_2} = [F_{IO_2} \times (P_B - P_{H_2O})] - (P_{aCO_2}/RER)$$

A–a gradient:

$$P_{AO_2} - P_{aO_2}$$

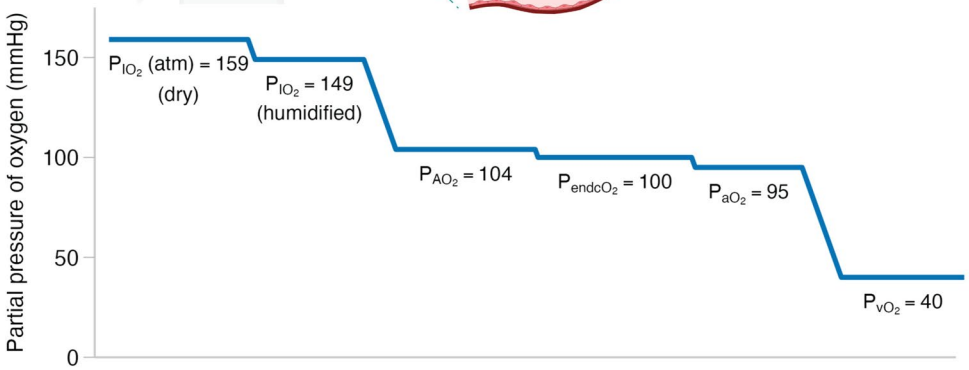

Fig. 1 Oxygen cascade and alveolar gas equation. **A** Determinants of oxygen partial pressure at each step of the oxygen cascade. **B** Corresponding physiologic values of oxygen partial pressure in a healthy adult breathing room air. Oxygen moves down a cascade of decreasing partial pressure from the atmosphere to end tissues. In the atmosphere, the oxygen partial pressure is the product of the barometric pressure and the fraction of inspired oxygen. As air enters the airway, it becomes fully humidified, taking up water vapor pressure and decreasing the oxygen partial pressure. Within the alveoli, two processes determine the alveolar partial pressure: alveolar ventilation, which delivers oxygen, and oxygen consumption, which removes it into the blood. The alveolar gas equation directly reflects these two processes: the first term represents the oxygen tension of inspired, fully humidified gas reaching the alveoli, whereas the latter term incorporates the arterial partial pressure of carbon dioxide and the respiratory exchange ratio, reflecting the oxygen uptake. Beyond the alveoli, oxygen diffuses into the pulmonary capillary—a process affected by ventilation–perfusion matching (common in critical illness) and the lungs' diffusion capacity (only rarely). This oxygenated blood then mixes with venous admixture from physiologic and pathologic shunts to constitute arterial blood. Consequently, the difference between alveolar and arterial oxygen partial pressures, the A–a gradient, indicates abnormalities in diffusion, ventilation–perfusion matching, or shunt. Finally, oxygen is delivered by the blood to peripheral tissues and extracted for cellular metabolism. P_{AO_2} (alveolar oxygen partial pressure); P_{aO_2} (arterial oxygen partial pressure); P_{IO_2} (inspired oxygen partial pressure); P_{IO_2} (inspired fraction of oxygen); P_{endcO_2} (pulmonary end-capillary oxygen partial pressure); P_{vO_2} (mixed venous oxygen partial pressure); P_B (barometric pressure); RER (respiratory exchange ratio). (Created in BioRender. https://BioRender.com/3jrsmkw)

Atmospheric pressure

Because P_B, and consequently P_{AO_2}, decreases linearly with increasing altitude, high-altitude exposure, flying in poorly pressurized cabins or helicopter transport, can cause hypoxemia. Supplemental oxygen readily restores P_{AO_2} to safe levels by compensating for the drop in P_B.

The AGE also explains why uncorrected P_{aO_2}/F_{IO_2} can be misleading for patients living at altitude. As P_B decreases, P_{AO_2} and P_{aO_2} fall proportionally, so indexing the P_{aO_2} with only F_{IO_2} can misclassify patients as hypoxemic despite preserved gas exchange relative to P_{AO_2} [5] Current consensus recommends either reporting P_B or

applying validated correction factors when interpreting P_{aO_2}/F_{IO_2} thresholds (e.g., for the diagnosis of ARDS) [6].

Arterial carbon dioxide partial pressure and respiratory exchange ratio

Because CO_2 and O_2 share the same alveolar space, any increase in the alveolar CO_2 (P_{ACO_2}) proportionally decreases P_{AO_2}. Due to the near-perfect diffusion property of CO_2, P_{aCO_2} closely reflects P_{ACO_2} and is used directly in the AGE. According to the equation, hypercapnia leads to a corresponding drop in P_{AO_2}; consequently, severe hypoventilation invariably results in hypoxemia (i.e., $P_{aO_2} < 60$ mmHg) even if the lungs are normal. Importantly, increasing ventilation to remove excess P_{ACO_2} improves oxygenation only in the cases of pure hypoventilation [7]. The AGE can be calculated in the presence of hypercapnia to explain whether the associated hypoxemia is only caused by hypoventilation or if low ventilation–perfusion ratios or shunts are present, as the latter are associated with a widened A–a gradient.

The RER modulates the effect of P_{aCO_2} on P_{AO_2}. As the lungs are the only organ exchanging both gases, alveolar RER reflects the body's respiratory quotient and varies depending on the metabolic substrate. When available, indirect calorimetry can determine RER and refine AGE estimation [8].

As an illustration, in patients receiving extracorporeal CO_2 removal ($ECCO_2R$), a significant portion of CO_2 is removed before reaching the alveoli, lowering RER and augmenting the impact of CO_2 on P_{AO_2} [9]. Due to the reduced RER, a physiologic P_{aCO_2} of 40 mmHg may result in dangerously low P_{AO_2}. Supplemental oxygen may not resolve hypoxemia completely as additional mechanisms can impair gas exchange (redistribution of perfusion, altered ventilation–perfusion relationships, or lung collapse associated with low minute ventilation) [10, 11]. If the reduced RER is not considered when calculating P_{AO_2}, spuriously widened A–a gradient may lead to overdiagnosis of these complications [12].

Similar physiological changes occur in patients receiving extracorporeal membrane oxygenation (ECMO), but their effects are less relevant because the membrane lung provides the majority of oxygenation.

P_{AO_2} and A–a gradient in the approach of hypoxemia and pulmonary shunt

The AGE provides an estimate of P_{AO_2}, allowing calculation of the A–a gradient, which quantifies the inadequacy of gas exchange. A normal A–a gradient is < 15 mmHg in young adults and < [age (in years)/4] + 4 in the elderly, reflecting poorer diffusion expected with aging. As discussed, reduced P_{AO_2} suggests alveolar hypoventilation (increased P_{aCO_2}) or reduced inspired oxygen pressure (e.g., high altitude). In contrast, preserved P_{AO_2} with a widened A–a gradient indicates impaired gas exchange, either due to ventilation–perfusion mismatch or right-to-left shunt. Although diffusion defect is a classic cause of hypoxemia (the term is sometimes used incorrectly) [16], diffusion impairment is rarely involved in critically ill patients and is mainly described in patients with pulmonary fibrosis, especially during exercise [13, 14].

The response to supplemental oxygen differentiates shunt from other mechanisms, as shunt is uniquely refractory to additional oxygen due to the bypass of venous admixture to systemic circulation [15, 16]. P_{aO_2}/F_{IO_2} measured under pure oxygen was shown to correlate well with pulmonary shunt due to nonaeration [17]. The AGE also provides the basis for calculating the pulmonary shunt fraction, as the pulmonary end-capillary oxygen pressure (P_{endcO_2}) approximates P_{AO_2} estimated by the equation. Using mixed venous blood sampling, quantification of shunt helps identify predominant shunt physiology in hypoxemic patients, where supplemental oxygen has limited effect and escalation of care may be needed [18].

Conclusions

- The AGE helps estimate P_{AO_2}, which is needed to identify ventilatory causes of hypoxemia. It explains the link between hypercapnia and hypoxemia.
- When interpreted alongside P_{aO_2} as the A–a gradient, it allows detection and quantification of impaired gas exchange.
- The AGE provides the physiological reference against which advanced interventions (e.g., high F_{IO_2} therapy, mechanical ventilation, $ECCO_2R$) should be interpreted, otherwise some conventional oxygenation indices could be misinterpreted in critically ill patients.

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Data availability
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